Enclosed herewith is a Supplemental Information Disclosure Statement, with references, for the Examiner's consideration.

CLAIM REJECTIONS – 35 USC §103

In the previous Office Action, claims 1, 7-12 and 14-19 were rejected under 35 USC §103(a) as being unpatentable over Doogan et al. (U.S. 4,962,128) in view of Howard et al. (U.S.5,597,826), and Pollinger et al. (U.S. 6,136,347). In the present Office Action, the rejection of claims 1, 7-12 and 14-19 under 35 USC §103(a) as being unpatentable over Doogan et al (U.S. 4,962,128) in view of Howard et al (U.S. 5,597,826) has been maintained for the reasons of the record in paper no. 9.

The Examiner has indicated that the Pollinger et al reference has been withdrawn as being a non-analogous art reference. Also, the Examiner noted Applicants' arguments in the previous response, but stated that the arguments were not persuasive.

First, according to the Examiner, Applicants argued that the Doogan et al. reference has failed to teach the preparation of non-aqueous liquid concentrate compositions of sertraline. However, the Examiner noted that the secondary Howard et al. reference supplements the primary reference and discloses that liquid preparations containing sertraline may be prepared by conventional means with pharmaceutically acceptable additives such as non-aqueous vehicles (see col. 22, lines 47-55). Therefore, the Examiner concludes that if the skillful artisan in the art had desired to develop the product containing nonaqueous liquid concentrate compositions of sertraline, it would have been obvious for the skillful artisan in the art to have motivated to incorporate Howard et al.'s nonaqueous vehicles into the Doogan et al. method because, for oral administration, Howard et al. does indicate that non-aqueous vehicles can be incorporated in the liquid preparations containing sertaline.

In response, Applicants would first point out that the Examiner has missed important differences between the pharmaceutical formulations described in Doogan et al. and the pharmaceutical formulations disclosed and claimed in the present application. The pharmaceutical formulations, which Doogan et al. are describing at col. 2, lines 63-64, are "aqueous suspensions and/or elixers [sic]" which are ready-to-use for oral administration. The claims of the present application are directed to pharmaceutical compositions which are essentially nonaqueous, liquid concentrates for oral administration. These concentrates are strong solutions which must be diluted in a suitable diluent or beverage prior to oral administration (see specification at page 6, lines 3-5; and page 8, lines 30-31). Nowhere does the Doogan et al. reference teach or suggest the preparation of liquid concentrate compositions of sertraline, much less essentially nonaqueous liquid concentrate compositions of sertraline, as claimed in the present application.

Second, Applicants would point out that the Howard et al. reference is directed to combination pharmaceutical therapy and discloses combination pharmaceutical compositions containing two active ingredients: 1) sertraline, or a pharmaceutically acceptable salt thereof, and 2) a compound of formula I, which is an agonist or antagonist of the serotonin 1 (5-HT_1) receptor. Furthermore, the non-aqueous vehicles, referred to by the Examiner in Howard et al., are to be included in conventional liquid preparations for the oral administration of the combination of the two active ingredients, as described above, and not for the administration of sertraline or its salts alone.

Therefore, because of these differences, Applicants would assert that the Examiner in this rejection has not properly combined these references, and the Howard et al. reference does not supplement the deficiencies of the Doogan et al. reference, as suggested by the Examiner.

However, for the sake of argument (and while not admitting that their combination is correct), if one of ordinary skill in the art were to combine these two references as suggested by the Examiner (i.e., incorporate Howard et al.'s nonaqueous vehicles (e.g. almond oil, oily ester or ethyl alcohol (at col. 22, lines 55-56)) into Doogan et al.'s aqueous formulations), logically, one would still have an aqueous formulation, but it would be an aqueous formulation (meaning one that contains water) having a nonaqueous vehicle as one of its components. The addition of the nonaqueous vehicle would not convert Doogan et al.'s aqueous formulation into a nonaqueous formulation, as suggested by the Examiner. Certainly, it would not convert Doogan et al.'s aqueous formulations into the essentially nonaqueous compositions of the present invention. And most certainly, it would not convert Doogan et al.'s aqueous, ready-to-use formulations into the essentially nonaqueous liquid concentrate compositions of the present invention, which must be diluted prior to use.

Therefore, Applicants would assert that the combination of the Doogan et al. reference and the Howard et al. reference, as suggested by the Examiner, do not render obvious the claims of the present invention.

Second, according to the Examiner, the Applicants argued that the Howard et al. reference has failed to teach the dose of sertraline or its salts. However, according to the Examiner, the Doogan et al reference does teach that it is administered in dosages ranging from 50-500 mg/day (see col. 2, lines 20-21); oral pharmaceutical formulations can be flavored by means of various agents; the composition contains sertraline with concentration levels ranging from 0.5% to 90% by weight of the total compositions (see col. 2, lines 45-46) or its pharmaceutically acceptable salt, flavoring agents, and diluents such as ethanol, propylene glycol, and glycerin (see from col. 2, line 65, to col. 3, line 2).

Also, according to the Examiner, the Howard et al. reference does teach the dose of 0.3 mg to 10 mg kg of body weight per day of the sertraline (see col. 23, lines 33-34). Furthermore, the Examiner states that it indirectly indicates that a dose ratio of sertraline to a compound of formula I in the formulation for oral administration is from 0.25 to 2,000 (see col. 24, lines 18-23). Therefore, the Examiner concludes that if the skillful artisan in the art had desired to develop the product containing non-aqueous liquid concentrate compositions of sertraline, it would have been obvious for the skillful artisan in the art to have motivated to use Howard et al's non-aqueous vehicles into the Doogan et al method because, for oral administration, Howard et al does indicate that non-aqueous vehicles can be incorporated in the liquid preparations containing sertraline.

In reply, Applicants would point out again (also as acknowledged by the Examiner above) that the Howard et al. reference discloses doses of sertraline only in combination with a second active ingredient, a compound of formula I. Also, as pointed out above, Doogan et al. discloses formulations of sertraline, which are different from the concentrate compositions of the present invention. Also, the dosage range disclosed by Doogan et al. and referenced by the Examiner, are different from the dosage range of sertraline hydrochloride in current claim 1, as previously amended, which is about 15 to about 30 mg/ml. In addition, as explained above, if one were to combine the references, as suggested by the Examiner, one would not achieve the essentially nonaqueous liquid concentrate compositions of the present invention.

Furthermore, as set forth in the specification as filed, Applicants have tried what was taught in the prior art. At page 3, lines 8-17, Applicants discuss the different dosage forms set forth in the prior art, including U.S. Patent No. 5,130,338, which discloses dosage forms that are very similar to those in the Doogan et al reference, cited by the Examiner.

In the specification, at page 3, lines 8-17, Applicants state that the '518 patent discloses that sertraline and related compounds can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. According to the '518 patent, when aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening, or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

However, Applicants note at page 3, lines 18-20, of the present specification, that development of an oral liquid dosage form of sertraline has been complicated by the

objectionable bitter taste and astringency sensation imparted by the drug in liquid form. Applicants further state at page 3, lines 20-23, of the specification, that direct ("ready-to-use") oral liquid solutions or suspensions of sertraline, such as those described in the '518 patent above (and in the Doogan et al. reference), have an objectionable taste, despite the inclusion of a variety of taste-masking or flavoring agents. Thus, Applicants have shown that the formulations, as suggested by the Examiner and the prior art, did not work satisfactorily for the present invention, further demonstrating the non-obviousness of the present invention.

Third, according to the Examiner, the Applicants have argued that applicants' non-aqueous liquid concentrate for oral administration having unique amount and combination of excipients have resulted in unexpected properties. However, the Examiner concludes that applicants' argument of unexpected results cannot take the place of evidence in the record.

Applicants would remind the Examiner that those unexpected properties are not just Applicants' arguments, but are set forth in the present specification as filed. Applicants would point to the present specification, especially page 6, lines 25-31, where they have shown that, in addition to acceptable taste upon administration, the essentially nonaqueous oral concentrate of the present invention has other surprising and unexpected advantages. It provides convenience in measuring different doses, which are needed for certain indications, as well as good physical/chemical stability characteristics throughout the product's shelf-life and use interval. Since the concentrate of the present invention is a solution, it is preferred over a suspension for ease of manufacture and optimal control of dosing homogeneity. Also, it provides for maximum solubilization of the sertraline hydrochloride drug substance (see the specification at page 7, lines 22-24). Thus, Applicants have created a nonconventional pharmaceutical composition which is an essentially nonaqueous liquid concentrate for oral administration, following dilution, having a unique amount and combination of excipients, resulting in surprising and unexpected properties, such as acceptable taste, stability, dosing homogeneity, and solubility, not taught or suggested by the prior art, and which is, therefore patentable over the prior art.

Fourth, according to the Examiner, Applicants have argued that the Examiner has not supplied the motivation to combine the references to achieve the non-conventional, non-aqueous liquid concentrate having the unique amounts and combination of excipients. However, according to the Examiner, there is motivation to combine the references. Doogan et al. does disclose the pharmaceutical composition containing sertraline hydrochloride (see col. 1, line 68) with a dose from 25 mg to 200 mg for treating anxiety-related disorders (see col. 2, lines 20-23); in addition, oral pharmaceutical formulations can be flavored by means of various agents; the composition contains sertraline or its pharmaceutically acceptable salt,

flavoring agents, and diluents such as ethanol, propylene glycol, and glycerin (see from col. 2, line 65, to col. 3, line 2). According to the Examiner, if elixirs are desired for oral administration, the sertraline may be combined with various flavoring agents 6 (see from col. 2., lines 63-67).

Furthermore, the Examiner has stated that Howard et al discloses expressly the pharmaceutical composition containing sertraline hydrochloride (see col. 20, line 31) with a dose from 0.1 mg to 200 mg (see col. 24, lines 7-8), suspending agents, non-aqueous vehicles such as ethyl alcohol, and preservatives (see col. 22, lines 51-56); in addition, oral pharmaceutical formulations can be flavored by means of various agents (see col. 23, lines 56-58). Also, the Examiner stated that the reference indicates that pharmacologically acceptable anions include methanesulfonate (see col. 20, lines 60-61).

Upon closer review of the Howard et al. reference, Applicants would like to correct several statements the Examiner has made with respect to this reference. As Applicants have explained above, the Howard et al. reference is directed to combination pharmaceutical therapy and discloses combination pharmaceutical compositions containing two active ingredients: 1) sertraline, or a pharmaceutically acceptable salt thereof, and 2) a compound of formula I, which is an agonist or antagonist of the serotonin 1 ($5\text{-}HT_1$) receptor. The dose, which the Examiner refers to at col. 24, lines 7-8, of the Howard et al. reference, is for doses of the compound of formula I, and not for sertraline or its salts. Furthermore, the suspending agents, non-aqueous vehicles and preservatives, referred to by the Examiner, are to be included in conventional liquid preparations for the oral administration of the combination of the two active ingredients, as described above, and not for the administration of sertraline or its salts alone. Furthermore, the reference at col. 20, lines 60-61, of the Howard reference to pharmacologically acceptable anions, including methanesulfonate, is to the preparation of salts of the compound of formula I, and not sertraline, which is claimed in claim 11 of the present application.

In the absence of Applicants' own disclosure, Applicants would assert that the Examiner has not supplied the requisite suggestion, teaching or motivation to combine the above cited references in order to achieve the nonconventional, essentially nonaqueous oral concentrate of the present invention having the unique amounts and combination of excipients. With the many differences pointed out above, Applicants have clearly distinguished the Doogan et al. reference and the Howard et al. reference, either singly or in combination, from the present invention. Furthermore, as explained above, Applicants have shown that if one were to combine the references, as suggested by the Examiner, one would not have the essentially nonaqueous liquid concentrate compositions of the present invention. Thus, Applicants would assert that claims 1, 7-12 and 14-19, as amended, are

patentable over the Doogan et al. reference and the Howard et al. reference under 35 USC §103(a).

In conclusion, the Examiner has stated that both [references] are definitively dealt with the pharmaceutical composition containing sertraline hydrochloride with an overlapping dose; both do describe that the pharmaceutical composition containing sertraline hydrochloride may be combined with various pharmaceutically acceptable inert carrier in the form of syrups and solutions. Therefore, the Examiner stated that if the skillful artisan in the art had desired to develop the product containing non-aqueous liquid concentrate compositions containing sertraline and methanesulfonate as pharmacologically acceptable anions, it would have been obvious for the skillful artisan in the art to have motivated to use Howard et al.'s methanesulfonate into the Doogan et al. pharmaceutical composition containing sertraline hydrochloride because, for oral administration, both do indicate that non-aqueous vehicles can be incorporated in the liquid preparations containing sertraline. Therefore, the Examiner concluded that there is the motivation to combine the references rejection references (*sic*) to achieve the non-aqueous liquid concentrate having the unique amounts and combination of excipients by routine experimentation.

As explained above, Applicants believe that there are many reasons why the present invention is distinguishable from the references cited above. As noted above, the reference in Howard et al. to pharmacologically acceptable anions, including methanesulfonate, is to the preparation of salts of the compound of formula I, and not sertraline. In addition, claim 1, as currently amended, is directed to the hydrochloride salt of sertraline. Furthermore, Applicants do not believe that the Examiner has met his burden of establishing a *prima facie* case of obviousness for the present invention with the references cited above.

To establish a *prima facie* case, the USPTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See, e.g., *Karsten Mf. Corp. v. Cleveland Gulf Co.*, 242 F3d. 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001). Above, Applicants have already addressed the lack of motivation to combine the references, as suggested by the Examiner, including showing, for argument's sake, that if one of ordinary skill in the art were to combine the references, as suggested by the Examiner, one would not achieve the concentrate compositions of the present invention.

Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. See, e.g.,

Amgen, Inc. v. Chugai Pharm. Co., 927 F2d. 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). As noted above and in the specification, Applicants had tried what was taught in the prior art with unsatisfactory results. Therefore, Applicants would assert there was not a reasonable expectation of success at the time the present invention was made.

Third, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F2d. 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A 1970). With the many differences pointed out above, Applicants have shown that the cited references, either alone or in combination, do not disclose or suggest all of the limitations of the current claims, especially claim 1, as amended. In addition, in the previous Office Action, the Examiner even admitted that the cited prior art is silent as to the claimed range of ethanol in glycerin, as claimed in the present application.

Therefore, Applicants do not believe the Examiner has established a *prima facie* case of obviousness for the claims of the present application. Thus, Applicants would assert that claims 1, 7-12 and 14-19, as amended, are patentable over the Doogan et al. reference and the Howard et al. reference, either singly or in combination, under 35 USC §103(a) and respectfully request that this rejection of the claims be withdrawn.

On the basis of the above remarks, Applicants respectfully request reconsideration of this application, as amended, and the early allowance of all the claims, including claims 1, 7-12 and 14-19, as amended.

Respectfully submitted,

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Attachments:
Petition for Extension of Time
Supplemental Information Disclosure Statement